Answer 1:

Bibliographic Information

Mouse mammary tumor virus promoter-containing retroviral promoter conversion vectors for gene-directed enzyme prodrug therapy are functional in vitro and in vivo. Klein, Reinhard; Ruttkowski, Baerbel; Schwab, Sonja; Peterbauer, Thomas; Salmons, Brian; Guenzburg, Walter H.; Hohenadl, Christine. Austrianova Biotechnology GmbH, Vienna, Austria. Journal of Biomedicine and Biotechnology (2008), No pp. given. Publisher: Hindawi Publishing Corp., CODEN: JBBOAJ ISSN: 1110-7251. http://www.hindawi.com/GetArticle.aspx?doi=10.1155/2008/683505 Journal; Online Computer File written in English. CAN 149:167378 AN 2008:782531 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Gene directed-enzyme prodrug therapy (GDEPT) is an approach for sensitization of tumor cells to an enzymically activated, otherwise nontoxic, prodrug. Cytochrome P 450 2B1 (CYP2B1) metabolizes the prodrugs cyclophosphamide (CPA) and ifosfamide (IFA) to produce the cytotoxic substances phosphoramide mustard and isophosphoramide mustard as well as the byproduct acrolein. We have constructed a retroviral promoter conversion (ProCon) vector for breast cancer GDEPT. The vector allows expression of CYP2B1 from the mouse mammary tumor virus (MMTV) promoter known to be active in the mammary glands of transgenic animals. It is anticipated to be used for the generation of encapsulated viral vector producing cells which, when placed inside or close to a tumor, will act as suppliers of the therapeutic CYP2B1 protein as well as of the therapeutic vector itself. The generated vector was effectively packaged by virus producing cells and allowed the prodn. of high levels of enzymically active CYP2B1 in infected cells which sensitized them to killing upon treatment with both IFA and CPA. Detn. of the resp. IC50 values demonstrated that the effective IFA dose was reduced by sixteen folds. Infection efficiencies in vivo were detd. using a reporter gene-bearing vector in a mammary cancer cell-derived xenograft tumor mouse model.

Answer 2:

Bibliographic Information

Impact of imatinib* on the pharmacokinetics and in vivo efficacy of etoposide and/or ifosfamide. Rezai, Keyvan; Lokiec, Francois; Grandjean, Isabelle; Weill, Sophie; de Cremoux, Patricia; Bordier, Vincent; Ekue, Richard; Garcia, Mickael; Poupon, Marie-France; Decaudin, Didier. Department of Pharmacology Oncology, Centre Rene Huguenin, Saint-Cloud, Fr. BMC Pharmacology (2007), 7 No pp. given. Publisher: BioMed Central Ltd., CODEN: BPMHBU ISSN: 1471-2210. http://www.biomedcentral.com/content/pdf/1471-2210-7-13.pdf Journal; Online Computer File written in English. CAN 148:229420 AN 2008:77247 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Using a human small cell lung cancer (SCLC) xenografted in nude mice, we have previously reported enhanced tumor growth inhibition following chemotherapy in combination with imatinib (STI571). We therefore investigated the in vivo impact of imatinib on the pharmacokinetics and efficacy of chemotherapy. Methods: Two different human tumors were used: SCLC6 small cell lung cancer xenografted in nude mice, and LY-3 EBV-assocd. human B-cell lymphoma xenografted in SCID mice. Plasma, urine, and fecal concns. of etoposide (VP16) were detd. by a validated high performance liq. chromatog. method. Plasma concns. of ifosfamide were detd. by a validated gas chromatog. assay with nitrogen-phosphorus detection. Results: Slight tumor growth inhibition was induced by imatinib administered alone in one in vivo EBV-assocd. B-cell lymphomatous xenograft. In contrast, an increase of the chemotherapy-induced antitumor effect was obsd. in the lymphoma model but not in a small cell lung cancer model when mice bearing human xenografted tumors were treated concomitantly by imatinib and chemotherapy. This antitumor effect was not influenced by concomitant administration of fluconazole. The AUC0-3h (Area Under the concn.-time Curve) of etoposide was increased when mice were treated with etoposide + imatinib due to decreased fecal excretion. In contrast, imatinib did not appear to influence the urinary excretion of etoposide, and concomitant administration of the CYP3A4 inhibitor, fluconazole, with imatinib did not modify the pharmacokinetics of etoposide plus imatinib alone. Conclusions: Altogether, these results therefore justify further prospective phase I and II clin. trials with combinations of etoposide-based chemotherapy and imatinib in patients with certain cancers, such as malignant lymphoma, with careful toxicol. monitoring.

Answer 3:

Bibliographic Information

Downregulation of angiogenic factors in Ewing tumor xenografts by the combination of human interferon-α or interferon-β with ifosfamide. Sanceau, Josiane; Wietzerbin, Juana. Institut National de la Sante et de la Recherche Medicale U365, Section Recherche, Institut Curie, Paris, Fr. Annals of the New York Academy of Sciences (2004), 1030(Signal Transduction Pathways, Chromatin Structure, and Gene Expression Mechanisms as Therapeutic Targets), 170-178. Publisher: New York Academy of Sciences, CODEN: ANYAA9 ISSN: 0077-8923. Journal written in English. CAN 142:441412 AN 2005:296767 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Ewing sarcoma is the second most common bone tumor in childhood. Despite aggressive chemotherapy and radiotherapy, the prognosis of metastatic disease remains poor. In a nude mouse model of Ewing tumor xenografts, we recently showed that human type I interferons (IFNs) inhibit the growth of established xenografts. Combined therapy with human IFNs and ifosfamide (IFO), an alkylating agent widely used in high-dose chemotherapy of Ewing tumors, results in a strong synergistic antitumor effect. We have investigated the effect of IFNs/IFO treatment on the expression of vascular endothelial growth factor (VEGF), matrix metalloproteinase 9 (MMP-9), and urokinase plasminogen activator receptor (uPAR), three key mediators of tumor growth and angiogenesis, in tumor xenografts generated either from a primary tumor (EW7) or from a metastatic tumor (COH). COH tumors expressed 5-fold higher levels of VEGF than EW7 tumors. IFNs/IFO treatment reduced by >70% the amt. of VEGF in COB and EW7 tumors. We did not detect constitutive MMP-9 activity in EW7 tumors. In contrast, the metastasis-derived COH tumor expressed very high levels of active MMP-9. Although the total amt. of MMP-9 remained unchanged, active MMP-9 was reduced by up to 75% in IFNs/IFO-treated COH tumors. IFNs/IFO treatment triggered in both COH and EW7 tumors the downregulation of uPAR expression, a mol. involved in vascularization and endothelial cell migration. Our results partly explain the mechanism of tumor growth inhibition by IFNs/IFO therapy and provide a rational foundation for the development of a new therapeutic approach to Ewing tumors resistant to conventional chemotherapy.

Answer 4:

Bibliographic Information

Human osteosarcoma xenografts and their sensitivity to chemotherapy. Bruheim, Skjalg; Bruland, Oyvind S.; Breistol, Knut; Maelandsmo, Gunhild M.; Fodstad, Oystein. Department of Tumor Biology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo, Norway. Pathology Oncology Research (2004), 10(3), 133-141. Publisher: Aranyi Lajos Foundation, CODEN: POREFR ISSN: 1219-4956. Journal written in English. CAN 142:253924 AN 2004:1018322 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Despite the increased survival rates of osteosarcoma patients attributed to adjuvant chemotherapy, at least one third of the patients still die due to their disease. Further improvements in the management of osteosarcoma may rely on a more individualized treatment strategy, as well as on the introduction of new drugs. To aid in the preclin. evaluation of new candidate substances against osteosarcoma, we have established 11 human osteosarcoma xenograft lines and characterized them with regard to response to five different ref. drugs. Doxorubicin, cisplatin methotrexate, ifosfamide and lomustine were effective in 3/11, 3/11,1/10, 5/11 and 4/11 of the xenografts, resp. Five xenografts were resistant to all compds. tested. We also assessed the mRNA expression levels of the xenografts for the O6-Methylguanine DNA Methyltransferase (MGMT), DNA topoisomerase II- (Topo II)-α, Gluthathione-S-transferase (GST)-π, Multidrug-resistance related protein (MRP) 1 and Multidrug-resistance (MDR) 1 genes. There was an inverse correlation between the transcript levels of GST-π and doxorubicin growth inhibition ($r = -0.66$; $p<0.05$), and between the transcript levels of MGMT and the effect of lomustine ($r = -0.72$; $p<0.01$), whereas the expression of MRP1 and cisplatin growth inhibition was pos. correlated ($r=0.82$; $p<0.005$). This panel of xenografts should constitute a good tool for pharmacol. and mol. studies in osteosarcoma.

Answer 5:

Bibliographic Information

Distinct Responses of Xenografted Gliomas to Different Alkylating Agents Are Related to Histology and Genetic Alterations. Leuraud, Pascal; Taillandier, Luc; Medioni, Jacques; Aguirre-Cruz, Lucinda; Criniere, Emmanuelle; Marie, Yannick; Kujas, Michele; Golmard, Jean-Louis; Duprez, Adrien; Delattre, Jean-Yves; Sanson, Marc; Poupon, Marie-France. Institut National de la Sante et de la Recherche Medicale, Laboratoire de Biologie des Interactions Neurones-Glie, Groupe Hospitalier Pitie-Salpetriere, Paris, Fr. Cancer Research (2004), 64(13), 4648-4653. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 141:116709 AN 2004:537842 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A series of 12 human gliomas was established as xenografts in nude mice and used to evaluate the relationship between histol., genetic parameters, and response to alkylating agents. Eight were high-grade oligodendroglial tumors, and four were glioblastoma. They were characterized for their genetic alterations, including those considered as "early" alterations, namely loss of chromosome 1 ± loss of chromosome 19q, TP53 mutation, and those considered as "late" alterations, namely loss of chromosome 10, loss of chromosome 9p, EGFR genomic amplification, PTEN mutation, CDKN2A homozygous deletion, and telomerase reactivation. Chemosensitivity of xenografts to four alkylating agents, temozolomide (42 mg/kg, days 1-5, p.o.), 1,3-bis(2-chloroethyl)-1-nitrosourea (5 mg/kg, day 1, i.p.), Ifosfamide (90 mg/kg, days 1-3, i.p.), and carboplatin (66 mg/kg, day 1, i.p.) was tested by administration of drugs to tumor-bearing mice. Although each tumor presented an individual response pattern, glioblastoma had a lower chemosensitivity than oligodendrogliomas, and temozolomide was the most effective drug. Deletion of 1p ± 19q was assocd. with higher chemosensitivity, whereas late mol. alterations, particularly EGFR amplification, were assocd. with chemoresistance. These results suggest that the combined use of histol. and mol. markers should eventually be helpful selecting the most appropriate agents for treatment of malignant oligodendrogliomas and astrocytomas.

Answer 6:

Bibliographic Information

Clonogenic assay with established human tumour xenografts: correlation of in vitro to in vivo activity as a basis for anticancer drug discovery. Fiebig, H. H.; Maier, A.; Burger, A. M. Oncotest GmbH, Institute for Experimental Oncology, Freiburg, Germany. European Journal of Cancer (2004), 40(6), 802-820. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 141:342988 AN 2004:284718 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pluripotent cells can be grown in clonogenic assays. The tumor stem-cell fraction, which accounts for <0.4% of the total cells, and which is considered the most relevant cell type in the development of metastases and recurrences, is able to divide and to form colonies in a semisolid matrix (agar or methylcellulose). Major applications of the tumor clonogenic assay (TCA) are chemosensitivity testing of tumors and xenografts, and for assessments within drug discovery programs. Of crit. relevance for the usefulness of the TCA is whether it can predict sensitivity or resistance towards clin. used agents. When we compared the response of human tumors established as xenografts in nude mice in the TCA in vitro to that of the clin. response, 62% of the comparisons for drug sensitivity, and 92% of the comparisons for drug resistance were correct. The same percentage of true/false observations was found when tumors were tested after serial passage in nude mice in the TCA in vitro and their response compared to in vivo activity in corresponding xenografts (60% and 90%, resp.). The highest correct predictive values were, however, found when the clin. response of tumors was compared to their explants established in the nude mouse and treated in vivo. Of 80 comparisons performed, we obsd. a correct prediction for tumor resistance in 97% and for tumor sensitivity in 90%. In our opinion, the TCA with established human tumor xenografts has an important role in current drug discovery strategies. We therefore included the TCA as secondary assay in our approach to anticancer drug discovery and found that a no. of novel agents were active; these are now in advanced preclin. development or clin. trials. Thus, the tumor clonogenic assay has proven predictive value in the chemosensitivity testing of std. and exptl. anticancer drugs.

Answer 7:

Bibliographic Information

Peripheral benzodiazepine receptor ligands reverse apoptosis resistance of cancer cells in vitro and in vivo. Decaudin, Didier; Castedo, Maria; Nemati, Fariba; Beurdeley-Thomas, Arnaud; De Pinieux, Gonzague; Caron, Antoine; Pouillart, Pierre; Wijdenes, John; Rouillard, Dany; Kroemer, Guido; Poupon, Marie-France. Departments of Hematology and UMR 147 CNRS, Section de Recherche, Institut Curie, Paris, Fr. Cancer Research (2002), 62(5), 1388-1393. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 137:134621 AN 2002:226277 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The mitochondrial peripheral benzodiazepine receptor (mPBR) is involved in a functional structure designated as the permeability transition pore, which controls apoptosis. Binding of Fas/APO-1/CD95 triggers a prototypic apoptosis-inducing pathway. Using four different human tumor cell lines (T-cell Jurkat, neuroblastoma SHEP, osteosarcoma 143N2, and glioblastoma SNB79 cell lines), all of which express CD95 and mPBR, the authors investigated the potential role of mPBR ligands in CD95-induced apoptosis. The authors show that, in vitro, the three mPBR ligands tested (RO5-4864, PK11195, and diazepam) enhanced apoptosis induced by anti-CD95 antibody in Jurkat cells, as demonstrated by mitochondrial transmembrane potential drop and DNA fragmentation. In contrast, RO5-4864, but not PK11195 or diazepam, enhanced anti-CD95 apoptosis in all other cell lines. These effects were obtained in Bcl-2-overexpressing SHEP cell lines, but not in Bcl-XL SHEP cell lines. Enhancement of anti-CD95 antibody-induced apoptosis by RO5-4864 was characterized by an increased mitochondrial release of cytochrome c and Smac/DIABLO proteins and an enhanced activation of caspases 9 and 3, suggesting a mitochondrion-dependent mechanism. Preincubation of cells with the different mPBR ligands or anti-CD95 did not affect the levels of expression of either mPBR or CD95. In vivo, the authors found that the RO5-4864 mPBR ligand significantly increased the growth inhibition induced by two chemotherapeutic agents, etoposide and ifosfamide, using two human small cell lung cancers xenografted into nude mice. Peripheral benzodiazepine receptor ligands may therefore act as chemosensitizing agents for the treatment of human neoplasms.

Answer 8:

Bibliographic Information

Distinctive potentiating effects of cisplatin and/or ifosfamide combined with etoposide in human small-cell lung carcinoma xenografts. Nemati, Fariba; Livartowski, Alain; De Cremoux, Patricia; Bourgeois, Yveline; Arvelo, Francisco; Pouillart, Pierre; Poupon, Marie-France. Centre National de la Recherche Scientifique, Institut Curie, Paris, Fr. Clinical Cancer Research (2000), 6(5), 2075-2086. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 133:275871 AN 2000:401148 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Xenografts (in mice) of small-cell lung carcinoma (SCLC) from eight patients were used to test the tumor sensitivity to etoposide (VP16; 12-16 mg/kg/day, days 1, 2, and 3), cisplatin (CDDP; 6-9 mg/kg/day, day 1) and ifosfamide (IFO; 90-210 mg/kg/day, days 1, 2, and 3) as single agents and to evaluate the efficacy of 2-drug or 3-drug combinations. Five xenografts came from untreated patients (SCLC-61, SCLC-6, SCLC-10, SCLC-41, and SCLC-96) and three after treatment (SCLC-74, SCLC-101, and SCLC-108). P53 was inactivated in all of them. Tumor growth inhibition, growth delay, and the survival rate of tumor-bearing mice reflected individual SCLC chemosensitivity. As single agents, IFO inhibited tumor growth in a dose-dependent manner, whereas CDDP and VP16 had little or no effect. Both CDDP and IFO potentiated VP16, inducing complete regressions in the most sensitive SCLCs; VP16-IFO was more effective than VP16-CDDP, with complete regressions in six vs. three of the eight tumors tested, resp. CDDP-IFO was less effective than VP16-IFO, with three of eight SCLCs giving complete regressions. The 3-drug combination led to modest improvement over the best 2-drug combination but only for sensitive SCLCs. Because the drug responses distinguished two classes of SCLCs, as sensitive or refractory, MDR1, glutathione S-transferase π, lung-related multidrug resistance protein, multidrug resistance protein, and topoisomerase IIα mRNA expression was studied by semiquant. reverse transcription. There was no correlation with SCLC sensitivity; topoisomerase IIα and multidrug resistance protein were expressed in all cases, lung-related multidrug resistance protein and

glutathione S-transferase π in seven of eight, and MDR1 gene in four of eight. In conclusion, these SCLC xenografts displayed a pattern of chemotherapy response close to that obsd. in patients.
This model confirmed that in 2-drug combinations, each component potentiated the effects of the other, with VP16-IFO tending to be the best 2-drug combination, both of which were more effective than VP16-CDDP and better tolerated than CDDP-IFO. The addn. of a 3rd agent gave only a modest, if any, therapeutic benefit in the responders but none in refractory SCLCs. There was no correlation between the extent of response and the expression of the resistance markers.

Answer 9:

Bibliographic Information

The effect of ifosfamide on tumor oxygenation at different temperatures. Mentzel, M.; Wiedemann, G.; Mendoza, A.S. Dept. of Physiology, Medical University of Luebeck, Germany. Advances in Experimental Medicine and Biology (1994), 345(Oxygen Transport to Tissue XV), 509-15. CODEN: AEMBAP ISSN: 0065-2598. Journal written in English. CAN 122:438 AN 1995:123847 CAPLUS

Abstract

In MX1 human breast cancer xenografts grown on the hind paw the thymus-aplastic nude mice the effect of ifosfamide on tumor oxygenation, tumor pH and the concn. of lactic acid were detd. at mean tumor temps. of 32°, 37°, and 41°. For histol. studies tumors were shock-frozen or fixed with formalin or glutaraldehyde. Treatment with ifosfamide decreased intratumoral laser Doppler flow, oxygenation and pH. This suggests that ifosfamide or its metabolites may have an effect on tumor vasculature.

Answer 10:

Bibliographic Information

The anti-tumor activity of ifosfamide on heterotransplanted testicular cancer cell lines remains unaltered by the uroprotector mesna. Bokemeyer, C.; Schmoll, H. -J.; Ludwig, E.; Harstrick, A.; Dunn, T.; Casper, J. Dep. Hematol., Hannover Univ. Med. Sch., Hannover, Germany. British Journal of Cancer (1994), 69(5), 863-7. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 121:169889 AN 1994:569889 CAPLUS

Abstract

Ifosfamide is clin. used in combination chemotherapy regimens for the treatment of patients with high-grade lymphomas, sarcomas and metastatic germ cell tumors. In order to reduce the oxazophosphorine-related urotoxicity, sodium mercaptoethane sulfonate (mesna) is used in different schedules following the administration of ifosfamide. The proposed mechanism of mesna activity is the binding of toxic oxazaphosphorine metabolites such as acrolein in the urine of the patients. Since an influence of mesna on ifosfamide anti-tumor activity is controversial, the current study has used xenografts from two human testicular cancer cell lines heterotransplanted into nude mice to study the anti-tumor activity of ifosfamide in combination with different dosages and schedules of mesna. In both human testicular cancer cell lines, H 12.1 and 2102 EP, ifosfamide demonstrated anti-tumor activity as a single agent. No redn. in ifosfamide activity was obsd. with the application of mesna at a dose range from 50% to 200% of the ifosfamide dose. Furthermore, the application of mesna before and 3 h after ifosfamide, a schedule used in many clin. protocols because of the short half life of mesna, not only maintained high ifosfamide anti-tumor activity but also seemed to be assocd. with the lower systemic and urotoxicity of ifosfamide therapy compared with ifosfamide given alone. In conclusion, the exptl. in vivo system using human heterotransplanted testicular cancer cell lines confirms the significant anti-tumor activity of ifosfamide in malignant germ cell tumors and demonstrates that mesna does not impair ifosfamide anti-tumor activity in this model. These results are most likely transferable to the use of mesna in patients with metastatic testicular cancer.

Answer 11:

Bibliographic Information

Local hyperthermia enhances cyclophosphamide, ifosfamide and cis-diamminedichloroplatinum cytotoxicity on human-derived breast carcinoma and sarcoma xenografts in nude mice. Wiedemann, Guenter; Roszinski, Stefan; Biersack, Anke; Weiss, Christoph; Wagner, Thomas. Dep. Intern. Med., Med. Univ. Luebeck, Luebeck, Germany. Journal of Cancer Research and Clinical Oncology (1992), 118(2), 129-35. CODEN: JCROD7 ISSN: 0171-5216. Journal written in English. CAN 120:153172 AN 1994:153172 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antitumor response and toxicity of locally applied hyperthermia with or without cyclophosphamide, ifosfamide, and cis-diamminedichloroplatinum (cisplatin) have been compared. The model systems were human breast carcinoma (MX1/3) and human sarcoma (S117) grown in nude mice. To detect changes of tumor oxygenation, intratumoral PO2 and pH were measured before, during and following hyperthermia. In both human tumor lines, a monotherapy with one of the cytotoxic drugs or with hyperthermia caused a transient growth delay, while the combination of the same dose of the drugs with hyperthermia (at 43° for 1 h) resulted in complete tumor remissions. During hyperthermia, in both tumor types, oxygenation was improved. Intratumoral pH remained practically unchanged.

Answer 12:

Bibliographic Information

Effects of temperature on the therapeutic efficacy and pharmacokinetics of ifosfamide. Wiedemann, G. J.; Siemens, H. J.; Mentzel, M.; Biersack, A.; Woessmann, W.; Knocks, D.; Weiss, C.; Wagner, T. Dep. Inte. Med., Med. Univ. Luebeck, Luebeck, Germany. Cancer Research (1993), 53(18), 4268-72. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 119:241045 AN 1993:641045 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The influence of tumor temp. (28, 32, 37, 39, 41, or 43° for 1 h) on the therapeutic efficacy of i.v. single bolus injections of ifosfamide (IFO) (32, 65, 125, or 250 mg/kg body wt.) in human tumor xenografts (MX1 breast carcinoma) growth in nude mice was studied. Tumor temp. was controlled by water bath immersion. Sixty days after treatment the percentage of tumor-free survival was detd. For example, 37° IFO at the dose of 65 mg/kg body wt. led to 10% tumor-free survival in the treated animals. At 43° the same dose resulted in 60% tumor-free survival. A clear drug dose- and temp.-dependent increase of the therapeutic efficacy of an active oxazaphosphorine compd. was also demonstrated in vitro. The concns. of IFO and 5-hydroxyifosfamide in blood and tumors at different body temps. (controlled by water bath immersion) were detd. over 120 min and WBC counts were obtained. The half-lives and the areas under the curve for IFO in blood were not significantly different at 37° and 41°. Since the half-life of IFO depends mainly on hepatic metab., the similarity of half-lives and of areas under the curve for IFO at 37° and 41° indicates a const. activation rate. However, significantly lower plasma concns. of the activated drug at a liver (body) temp. of 41°, compared with 37°, were found, indicating a higher elimination rate. The concn. of the activated drug in the tumors within the initial 60 min at 41°, however, exceeded by >2-fold that at 37°. The bone marrow toxicity of the same drug dose did not significantly increase with body temp.

Answer 13:

Bibliographic Information

Therapeutic outcome and side-effects after radiotherapy, chemotherapy and/or hyperthermia treatment of head and neck tumour xenografts. Ressel A; Schmitt O; Weiss C; Feyerabend T Department of Radiotherapy and Nuclear Medicine, University of Lubeck, Ratzeburger Allee 160, D-23538, Lubeck, Germany European journal of cancer (Oxford, England : 1990) (2002), 38(4), 594-601. Journal code: 9005373. ISSN:0959-8049. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11872355 AN 2002137490 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The aim of the study was to optimise the still unsatisfactory therapeutic results in head and neck cancer by studying the results and the side-effects of radiotherapy, chemotherapy and/or local hyperthermia treatment of human tumour xenografts. Mice carrying human-derived head and neck squamous cell carcinoma xenografts with a mean volume of 100 mm(3) received 5x2 Gy, cisplatin or ifosfamide and/or local hyperthermia at 41/41.8 degrees C. Haematocrit and tumour volumes were determined two or three times per week, respectively, until day 25 or day 60. At day 60, the highest number of complete remissions (CRs) (80%) was observed in the triple modality therapy group with radiation, local hyperthermia at 41.8 C and cisplatin at a dosage of 2 mg/kg body weight (b.w.). Therapeutic side-effects were moderate weight loss and a mild anaemia. Thus, with regard to the long-term tumour-free survival, the most effective treatment was the combination of radiotherapy, cisplatin and local hyperthermia at 41.8 C.

Answer 14:

Bibliographic Information

Preclinical phase II study of ifosfamide in human tumour xenografts in vivo. Berger D P; Fiebig H H; Winterhalter B R; Wallbrecher E; Henss H Department of Internal Medicine, University of Freiburg, Federal Republic of Germany Cancer chemotherapy and pharmacology (1990), 26 Suppl S7-11. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2347054 AN 90268681 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The in vivo effects of the oxazaphosphorine compound ifosfamide (IFO) on human tumour xenografts were assessed in thymus aplastic nude mice. The human origin of the tumours was confirmed by isoenzymatic and immunohistochemical methods. Tumour models were selected from a panel of 180 regularly growing, well-characterized xenografts. The maximum tolerated dose in tumour-bearing nude mice was determined to be 130 mg/kg per day given on days 1-3 and 15-17. After 21 days, lethality was 14% after i.p. and 6% after s.c. administration. A total of 43 human tumours were tested for antineoplastic activity, 15 of which (36%) showed regression: 4/5 breast cancer xenografts, 1/3 colon, 1/1 gastric, 2/7 non-small-cell lung cancers (NSCLC), 3/4 small-cell lung cancers (SCLC), 1/2 sarcomas and 3/3 testicular cancers. Two ovarian, two uterine and six renal cancer xenografts as well as three melanomas and five tumours of various histologies were resistant. In 30 human tumour xenografts, the antineoplastic efficacy of the two oxazaphosphorine derivatives cyclophosphamide and IFO was compared. The maximum tolerated dose of cyclophosphamide was 200 mg/kg per day given i.p. on days 1 and 15; it led to 17% lethality after 21 days. Cyclophosphamide induced tumour regression or remission in 10/30 xenografts (33%) and IFO in 13/30 (43%). In conclusion, the observed efficacy of IFO parallels the clinical situation. Breast, lung and testicular cancer and sarcomas proved to be responsive. The antitumoural activity of IFO shows similarities to that of cyclophosphamide; however, a higher response rate and lower toxicity were noted for the former. Preclinical phase II studies in nude mice seem to offer an effective way of identifying active drugs as well as sensitive tumour types for further clinical development.

Answer 15:

Bibliographic Information

Chemotherapy-radiation interactions in human cervix carcinoma xenografts. Tonkin K S; Kelland L R; Steel G G Radiotherapy Research Unit, Institute of Cancer Research, Sutton, Surrey, UK British journal of cancer (1988), 58(6), 738-41. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 2465016 AN 89134673 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The combination of irradiation and four agents of clinical interest in the treatment of cervix carcinoma (bleomycin, etoposide, cisplatin and ifosfamide) have been investigated using two human cervix carcinoma xenografts in nude mice. As a model of clinical brachytherapy regimes, radiation was administered at a continuous low dose rate of 5 cGy min-1 to a total dose of 9 or 12 Gy. No substantial enhancement in tumour growth delay over that observed for radiation alone was observed with bleomycin, etoposide or cisplatin. Ifosfamide, however, led to substantial additional growth delay, an effect which was lost when irradiation was administered at a higher dose rate of 70 cGy min-1. As dose-rates of around 5 cGy min-1 allow greater repair of radiation damage than at the higher dose-rate without significant cell cycling or repopulation, it is possible that ifosfamide may act as an inhibitor of repair processes in this model. It would be of interest to evaluate the role of ifosfamide and brachytherapy regimes in the clinical treatment of carcinoma of the cervix.